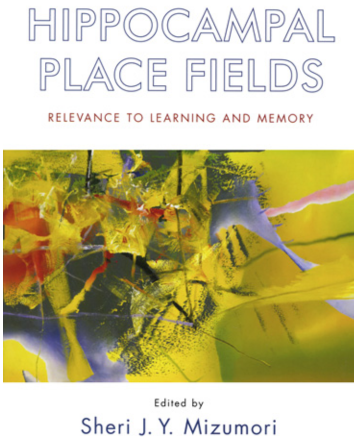
Neuron
Book Review

Place Cells in Perspective



Hippocampal Place Fields: Relevance to Learning and Memory

Edited by Sheri Mizumori
Oxford University Press (2008)
432 pp., $98.50, hardcover.

The importance of the hippocampus for learning and memory was first recognized in the late 1950s when William Scoville and Brenda Milner published their account of patient H.M. whose hippocampus was removed during an operation aimed at treating his otherwise intractable epilepsy. The operation was a success as far as the epilepsy was concerned, but there was an unexpected and very unfortunate side effect for H.M.: he lost his ability to form new memories for facts and events. Subsequent studies documenting spatial and nonspatial memory impairments in rodents and primates as a result of hippocampal damage made it clear that something that happens within the hippocampus or perhaps between the hippocampus and the neocortex makes it possible to store new memories for facts and events.

Efforts to understand how the hippocampus might allow for rapid memory storage included recording studies that sought to identify the neural firing patterns that underlie memory storage or retrieval. Given that the hippocampus is about as synaptically distant from both the sensory and the motor periphery as it is possible to be in the brain, there was no particular reason to expect that the neurons there would fire in response to easily identifiable external stimuli. Indeed, early efforts to understand hippocampal neural activity in the rat reported a wide variety of behavioral correlates and few common features. Even when, in 1971, O'Keefe and Dostrovsky published the first account of hippocampal neurons as "place cells," it was not yet clear to the field that spatial selectivity could explain (or at least describe) one of the key properties of hippocampal neural activity. Thirty-seven years later, the fact that active hippocampal neurons frequently fire in a restricted region of the animal's environment known as a "place field" is no longer in question. The link between these place cells and the mnemonic function of the hippocampus is still somewhat unclear, however, and *Hippocampal Place Fields: Relevance to Learning and Memory* serves as a reminder of both what we know and how much more there is for us to understand.

Sheri Mizumori has done an excellent job assembling and contributing to a large group of diverse and thoughtful essays on the relationship between hippocampal neural activity and learning and memory. The book is divided into five sections, and each section is made up of two or more chapters from different research groups. The result is that each chapter presents both a review of a subset of the available data as well as the authors' own perspective, giving the reader an unusual and worthwhile opportunity to sample the more speculative thought processes of a diverse group of researchers. The first two sections discuss results from recordings in rodent and primate hippocampus in relation to learning, memory, and spatial navigation. A few chapters deal in whole or in part with the issue of learning. These include a chapter from Mizumori outlining a model that describes how different types of information might be combined during learning and a chapter from Suzuki describing the advances her laboratory has made in understanding how hippocampal neurons change as new associations are learned.

The majority of the chapters deal with issues more directly related to representation and thus relate more directly to previously stored memories. These authors discuss results from recordings in familiar situations where they examine hippocampal activity as a window into the internal representation of the animal's environment. In the first chapter, for example, Nadel discusses the essential role of the hippocampus in encoding context, which he defines as the sets of relationships among the various cues in the environment, and particularly the relationships among the more temporally and spatially stable cues. From this perspective, the ensemble of place cells active in any given environment is an essential element of the animal's representation of the context, and changes in the activity of that ensemble represent changes in the context as experienced by the animal. Several of the following chapters echo that theme, in that the authors present data consistent with the idea that rodent hippocampal place cells constitute a representation of context that is used to guide behavior. Similarly, Nishito et al. and Rolls show that primate hippocampal neurons can fire in relationship to where the animal is in space or where it is looking. These results are consistent with a broad perspective on hippocampal memory encoding as discussed in a chapter by Eichenbaum and suggest that hippocampal activity is likely to be useful for memory-guided decision making.

The direct link between patterns of hippocampal activity and behavior remains to be established, however. This point is nicely illustrated in the Ainge et al. chapter. In the late 1990s, Emma Wood and I carried out simultaneous studies showing that hippocampal neural activity carries information not only about the animal's current location, but also about past or intended future positions. Thus, these cells were more than place cells, as they linked past, present, and future, and it seemed reasonable to us that this sort of activity might explain how hippocampal activity could guide behavior. Ainge et al., referring to this type of activity as context dependent, describe a series of studies they carried out to test the hypothesis that context-dependent activity was a central component of the hippocampal contribution to behavior. Sadly, this appealing ideal turns out to be, if not wrong, at least unlikely to be right. They show that context-dependent activity was prevalent in a task that does not require the hippocampus but was almost entirely absent following the addition of a delay that made the task sensitive to hippocampal damage.

This surprising result illustrates one of the main challenges facing the field of place cell research: figuring out exactly what it is that place cells are good for. It seems likely that the spatial firing of place cells is useful for something, but it is not clear how place cell output might eventually translate to differences in patterns of activity in motor planning areas that lead to overt behaviors. Many of the chapters in the third, fourth, and fifth sections of the book can been seen as efforts to begin to address this issue. These include a cogent review of entorhinal grid cells and their interactions with hippocampal place cells from Fynn et al. as well as an illuminating discussion of the contrast between neural activity in the hippocampus as compared to activity in the striatum and prefrontal cortex by Battaglia et al. There is also a section devoted to models of the hippocampus that explores the contributions of the various hippocampal subfields to memory storage (Papp and Treves), a model of the hippocampus and entorhinal cortex that seeks to explain how the place cells might guide behavior (Griffen et al.), and a model that explains how the distances between locations might be stored in the strengths of synapses between place fields (Csizmadia and Muller). Finally, the last two chapters discuss another very important element of the place cell story: the relationship between age-related memory impairments and changes in place field properties. Both chapters make a compelling and well-reasoned argument that differences in place cell activity at both the single cell (Wilson and Tanila) and ensemble level (Burke and Barnes) are related to older animals' memory problems.

And yet, as I ponder the state of our field, the reminder from Ainge et al. that correlation is not causation keeps coming to mind. So what, then, do we need to do to understand how hippocampal neural activity contributes to behavior? My sense is that we need to expand our efforts to manipulate hippocampal activity. The idea of altering activity is not new, of course, and two of the chapters in this book describe the effects of pharmacological manipulations such as dopamine (Gill and Mizumori) and NMDA receptor blockade (Rowland and Kentros) on place cells. These manipulations have been very informative, but they lack the temporal and spatial resolution that may be required to sort out what sorts of hippocampal activity are important for behavior. My hope is that as viral and genetic technologies improve, we will be able to identify and perturb specific patterns of activity in the hippocampus and record from downstream structures to understand how those perturbations affect processing in other brain areas. I believe that tracing these changes through the circuitry from the hippocampus to the motor periphery is perhaps our best bet for coming to understand how hippocampal activity contributes to learning and memory.

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